

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Gerhard Siemeister et al.

Group Art Unit:

Serial No.: To be assigned

Examiner:

Filed: Herewith

For: COMBINATIONS AND COMPOSITIONS WHICH INTERFERE WITH
VEGF/VEGF AND ANGIOPOIETIN/TIE RECEPTOR FUNCTION AND
THEIR USE

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

9. (Amended) Pharmaceutical compositions according to claim 1 which are intended for simultaneous or separate sequential therapeutical application.

10. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound I at least one of

- a) compounds which inhibit receptor tyrosine kinase activity,
- b) compounds which inhibit ligand binding to receptors,
- c) compounds which inhibit activation of intracellular signal pathways of the receptors,

- d) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- e) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

11. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound II at least one of

- f) compounds which inhibit receptor tyrosine kinase activity,
- g) compounds which inhibit ligand binding to receptors,
- h) compounds which inhibit activation of intracellular signal pathways of the receptors,
- i) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- j) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,

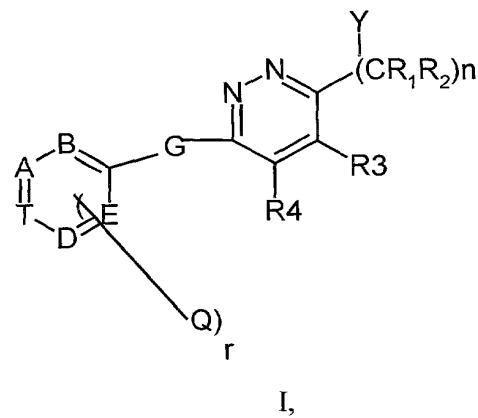
delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

12. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound I and/ or II at least one of Seq. ID Nos. 1-59.

13. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound I and/ or II Seq. ID Nos. 34a.

14. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound I and/ or II at least one of sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTFconjugate.

15. (Amended) Pharmaceutical compositions according to claim 1 which comprise as compound I and/ or II at least one small molecule of general formula I



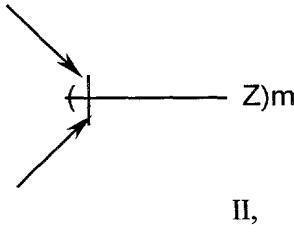
in which

r has the meaning of 0 to 2;

n has the meaning of 0 to 2;

R₃ und R₄ a) each independently from each other have the meaning of lower alkyl,
b) together form a bridge of general partial formula

II,

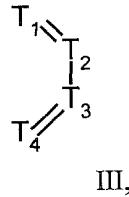


wherein the binding is via the two terminal C- atoms,

and

m has the meaning of 0 to 4; or

c) together form a bridge of partial formula III



III,

wherein one or two of the ring members T_1, T_2, T_3, T_4 has the meaning of nitrogen, and each others have the meaning of CH, and the bining is via the atoms T_1 and T_4 ;
 T_1 has the meaning of $C_1 - C_6$ - alkyl, $C_2 - C_6$ – alkylene or $C_2 - C_6$ – alkenylene; or $C_2 - C_6$ - alkylene or $C_3 - C_6$ - alkenylene, which are substituted with acyloxy or hydroxy; $-CH_2-O-$, $-CH_2-S-$, $-CH_2-NH-$, $-CH_2-O-CH_2-$, $-CH_2-S-CH_2-$, $-CH_2-NH-CH_2$, oxa (-O-), thia (-S-) or imino (-NH-),

A, B, D, E and T independently from each other have the meaning of N or CH₂, with the proviso that not more than three of these Substituents have the meaning of N,

Q has the meaning of lower alkyl, lower alkyloxy or halogene,

R₁ and R₂ independently from each other have the meaning of H or lower alkyl,

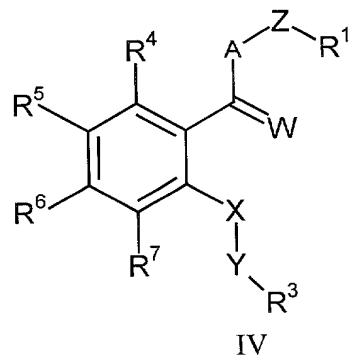
X has the meaning of imino, oxa or thia;

Y has the meaning of hydrogen, unsubstituted or substituted aryl, heteroaryl, or unsubstituted or substituted cycloalkyl; and

Z has the meaning of amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower-alkyl-thio, alkyl-phenyl-thio, phenylsulfinyl, phenyl-lower-alkyl-sulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower-alkan-sulfonyl, or alkylphenylsulfonyl,

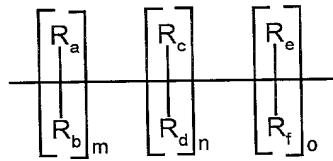
whereas, if more than one rest Z is present ($m \geq 2$), the substituents Z are equal or different from each other,

and wherein the bonds marked with an arrow are single or double bonds; or an N-oxide of said compound, wherein one or more N-atoms carry an oxygen atom, or a salt thereof, and/or a compound of general formula IV

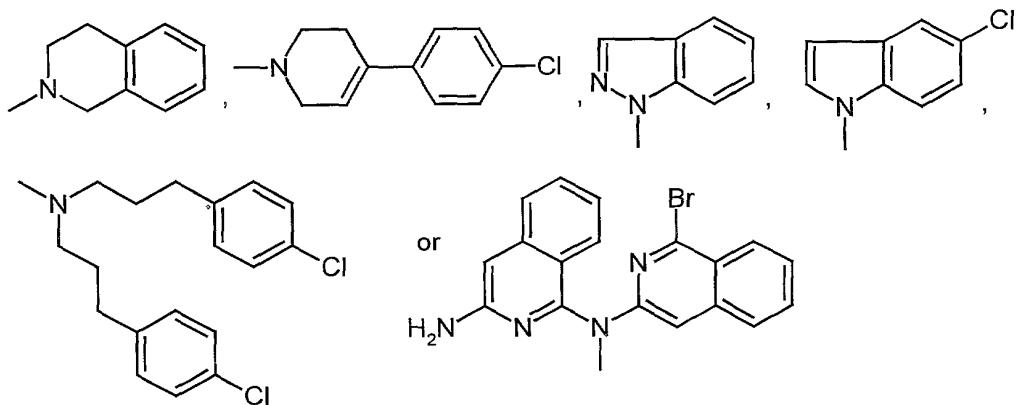


in which

- A has the meaning of group $=NR^2$,
- W has the meaning of oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,
- Z has the meaning of the group $=NR^{10}$ or $=N-$, $-N(R^{10})-(CH_2)_q-$, branched or unbranched C₁₋₆-Alkyl or is the group

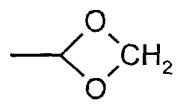


or A, Z and R¹ together form the group



m, n and o	has the meaning of 0 – 3,
q	has the meaning of 1 – 6,
R _a , R _b , R _c , R _d , R _e , R _f	independently from each other have the meaning of hydrogen, C ₁₋₄ alkyl or the group =NR ¹⁰ , and/ or R _a and/ or R _b together with R _c and or R _d or R _c together with R _e and/ or R _f form a bound, or up to two of the groups R _a -R _f form a bridge with each up to 3 C-atoms with R ¹ or R ² ,
X	has the meaning of group =NR ⁹ or =N-,
Y	has the meaning of group -(CH ₂) _p ,
p	has the meaning of integer 1-4,
R ¹	has the meaning of unsubstituted or optionally substituted with one or more of halogene, C ₁₋₆ -alkyl, or C ₁₋₆ -alkyl or C ₁₋₆ -alkoxy, which is optionally substituted by one or more of halogen, or is unsubstituted or substituted aryl or heteroaryl,
R ²	has the meaning of hydrogen or C ₁₋₆ -alkyl, or form a bridge with up to 3 ring atoms with R _a -R _f together with Z or R ₁ ,
R ³	has the meaning of monocyclic or bicyclic aryl or heteroaryl which is unsubstituted or optionally substituted with one or more of halogen, C ₁₋₆ -alkyl, C ₁₋₆ -alkoxy or hydroxy,
R ⁴ , R ⁵ , R ⁶ and R ⁷	independently from each other have the meaning of hydrogen, halogene or C ₁₋₆ -alkoxy, C ₁₋₆ -alkyl or C ₁₋₆ -carboxyalkyl, which are unsubstituted or optionally substituted with one

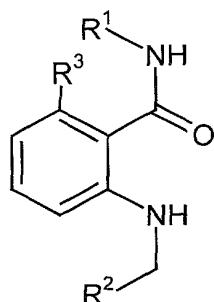
or more of halogene, or R⁵ and R⁶ together form the group



R⁸, R⁹ and R¹⁰ independently from each other have the meaning of hydrogen or C₁₋₆-alkyl,
as well as their isomers and salts,

and/ or a compound of general formula V

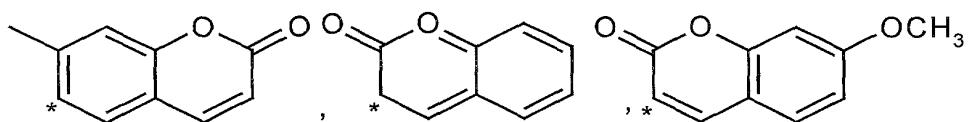
Invention relating to a compound of general formula V, or a salt thereof, and to its use in the preparation of medicaments.

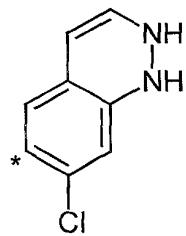
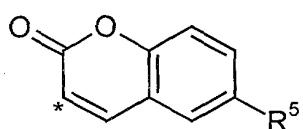


V,

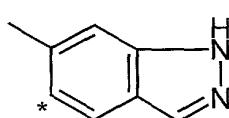
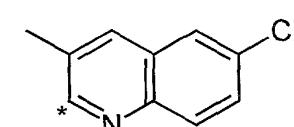
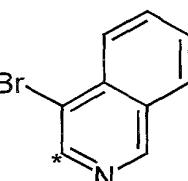
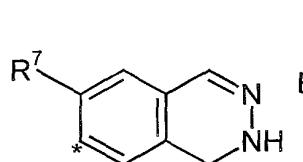
in which

R¹ has the meaning of group

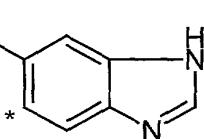
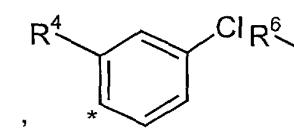
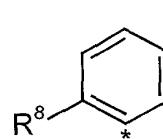
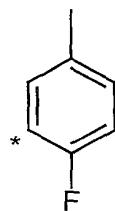




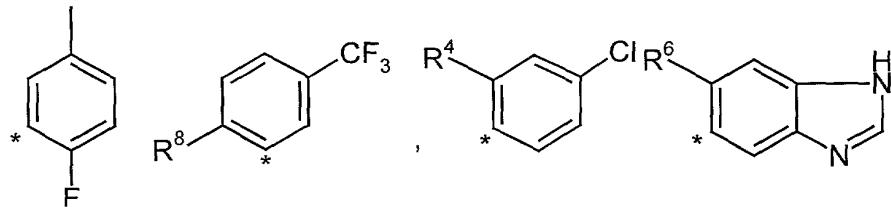
in which R^5 is chloro, bromo or the group -OCH₃,



in which R^7 is -CH₃ or chloro,



in which R⁷ is -CH₃ or chloro,

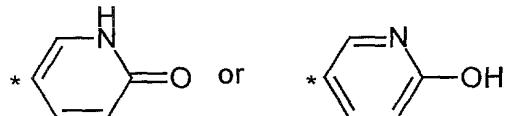


in which R⁸ is -CH₃, fluoro,
chloro or -CF₃

in which R⁴ is fluoro,
chloro, bromo, -CF₃,
-N=C, -CH₃, -OCF₃ or
-CH₂OH

in which R⁶ is
-CH₃ or chloro

R² has the meaning of pyridyl or the group



and

R³ has the meaning of hydrogen or fluoro, as well as their isomers and salts.

17. (Amended) Pharmaceutical compositions according to claims 1-16 which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, and as compound II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, with the proviso that compound I is not identically to compound II.

18. (Amended) Pharmaceutical compositions according to claims 1-17 which

comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate and as compound II sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate.

19. (Amended) Pharmaceutical compositions according to claims 1-17 which comprise as compound I mAB 4301-42-35 and as compound II sTie2, and/ or scFv-tTF conjugate.

20. (Amended) Pharmaceutical compositions according to claims 1-17 which comprise as compound I scFv-tTF conjugate and as compound II sTie2 and/ or mAB 4301-42-35.

21. (Amended) Pharmaceutical compositions according to claims 1-17 which comprise as compound I L19 scFv-tTF conjugate and as compound II sTie2.

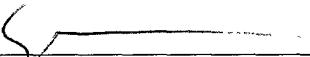
22. (Amended) Use of pharmaceutical compositions according to claims 1-21, for the production of a medicament for the treatment of tumors, cancers, psoriasis, arthritis, such as rheumatoide arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, kidney diseases, such as glomerulonephritis, diabetic nephropathie, maligneous nephrosclerosis, thrombic microangiopathic syndrome, transplantation rejections and glomerulopathy, fibrotic diseases, such as cirrhotic liver, mesangial cell proliferative diseases, arteriosclerosis, damage of nerve tissues, suppression of the ascites formation in patients and suppression of VEGF oedemas.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to cancelled combined subject matter.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,


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Attorney Docket No.: SCH-1815

Date: June 25, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

9. (Amended) Pharmaceutical compositions according to claim[s] 1[-8] which are intended for simultaneous or separate sequential therapeutical application.

10. (Amended) Pharmaceutical compositions according to claim[s] 1[-8] which comprise as compound I at least one of

- k) compounds which inhibit receptor tyrosine kinase activity,
- l) compounds which inhibit ligand binding to receptors,
- m) compounds which inhibit activation of intracellular signal pathways of the receptors,
- n) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- o) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,

delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

11. (Amended) Pharmaceutical compositions according to claim[s] 1[-8] which comprise as compound II at least one of

- p) compounds which inhibit receptor tyrosine kinase activity,
- q) compounds which inhibit ligand binding to receptors,
- r) compounds which inhibit activation of intracellular signal pathways of the receptors,
- s) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system,

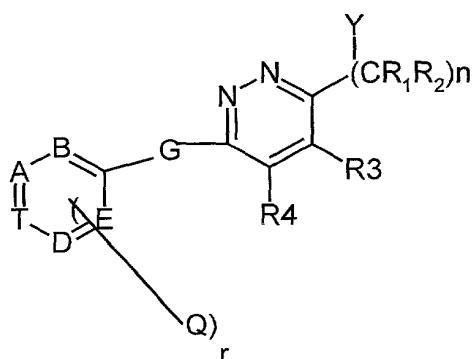
t) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

12. (Amended) Pharmaceutical compositions according to claim[s] 1[-11] which comprise as compound I and/ or II at least one of Seq. ID Nos. 1-59.

13. (Amended) Pharmaceutical compositions according to claim[s] 1[-11] which comprise as compound I and/ or II Seq. ID Nos. 34a.

14. (Amended) Pharmaceutical compositions according to claim[s] 1[-11] which comprise as compound I and/ or II at least one of sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTFconjugate.

15. (Amended) Pharmaceutical compositions according to claim[s] 1[-11] which comprise as compound I and/ or II at least one small molecule of genaral formula I



I,

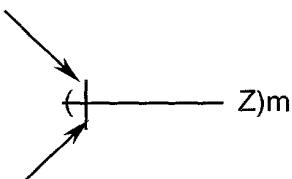
in which

- r has the meaning of 0 to 2,
- n has the meaning of 0 to 2;

R₃ und R₄

- a) each independently from each other have the meaning of lower alkyl,
- b) together form a bridge of general partial formula

II,



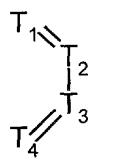
II,

wherein the binding is via the two terminal C- atoms,

and

- m has the meaning of 0 to 4; or

c) together form a bridge of partial formula III



III,

wherein one or two of the ring members T₁, T₂, T₃, T₄ has
the meaning of nitrogen, and each others have the
meaning of CH, and the bining is via the atoms T₁ and T₄;

G has the meaning of C₁ - C₆ - alkyl, C₂ - C₆ - alkylene or
C₂ - C₆ - alkenylene; or C₂ - C₆ - alkylene or C₃ - C₆-
alkenylene, which are substituted with acyloxy or
hydroxy; -CH₂-O-, -CH₂-S-, -CH₂-NH-, -CH₂-O-CH₂-,
-CH₂-S-CH₂-, -CH₂-NH-CH₂, oxa (-O-) or
imino (-NH-),

A, B, D, E and T independently from each other have the meaning of N
or CH, with the proviso that not more than three of
these Substituents have the meaning of N,

Q has the meaning of lower alkyl, lower alkyloxy or
halogene,

R₁ and R₂ independently from each other have the meaning of H
or lower alkyl,

X has the meaning of imino, oxa or thia;

Y has the meaning of hydrogene, unsubstituted or
substituted aryl, heteroaryl, or unsubstituted or
substituted cycloalkyl; and

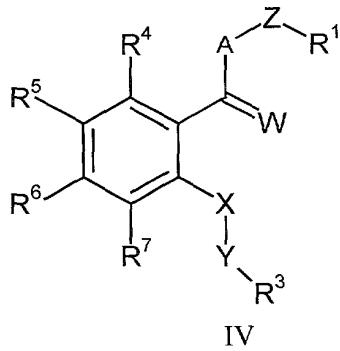
Z has the meaning of amino, mono- or disubstituted amino, halogen,
alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy,

esterified carboxy, alkanoyl, carbamoyl, N-mono- or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower-alkyl-thio, alkyl-phenyl-thio, phenylsulfinyl, phenyl-lower-alkyl-sulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower-alkan-sulfonyl, or alkylphenylsulfonyl,

whereas, if more than one rest Z is present ($m \geq 2$), the substituents Z are equal or different from each other,

and wherein the bonds marked with an arrow are single or double bonds; or an N-oxide of said compound, wherein one or more N-atoms carry an oxygen atom, or a salt thereof,

and/or a compound of general formula IV

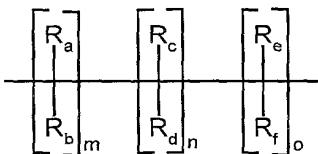


in which

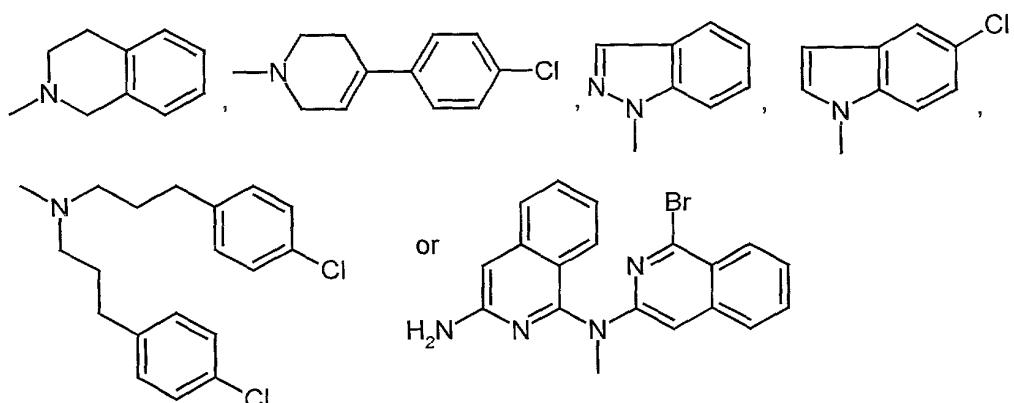
A has the meaning of group $=NR^2$,

W has the meaning of oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,

Z has the meaning of the group $=NR^{10}$ or $=N-(R^{10})-(CH_2)_q-$, branched or unbranched C₁₋₆-Alkyl or is the group



or A, Z and R¹ together form the group



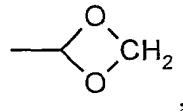
m, n and o	has the meaning of 0 – 3,
q	has the meaning of 1 – 6,
R _a , R _b , R _c , R _d , R _e , R _f	independently from each other have the meaning of hydrogen, C ₁₋₄ alkyl or the group =NR ¹⁰ , and/ or R _a and/ or R _b together with R _c and or R _d or R _c together with R _e and/ or R _f form a bound, or up to two of the groups R _a -R _f form a bridge with each up to 3 C-atoms with R ¹ or R ² ,
X	has the meaning of group =NR ⁹ or =N-,
Y	has the meaning of group -(CH ₂) _p ,
p	has the meaning of integer 1-4,

R¹ has the meaning of unsubstituted or optionally substituted with one or more of halogene, C₁₋₆-alkyl, or C₁₋₆-alkyl or C₁₋₆-alkoxy, which is optionally substituted by one or more of halogen, or is unsubstituted or substituted aryl or heteroaryl,

R² has the meaning of hydrogen or C₁₋₆-alkyl, or form a bridge with up to 3 ring atoms with R_a-R_f together with Z or R_j,

R³ has the meaning of monocyclic or bicyclic aryl or heteroaryl which is unsubstituted or optionally substituted with one or more of halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or hydroxy,

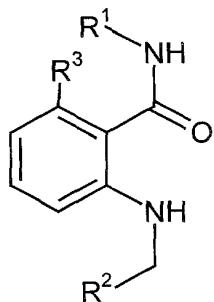
R⁴, R⁵, R⁶ and R⁷ independently from each other have the meaning of hydrogen, halogene or C₁₋₆-alkoxy, C₁₋₆-alkyl or C₁₋₆-carboxyalkyl, which are unsubstituted or optionally substituted with one or more of halogene, or R⁵ and R⁶ together form the group



R⁸, R⁹ and R¹⁰ independently from each other have the meaning of hydrogen or C₁₋₆-alkyl, as well as their isomers and salts,

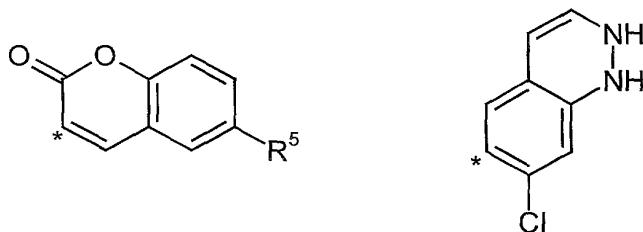
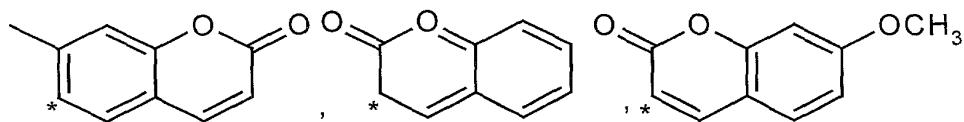
and/ or a compound of general formula V

V,

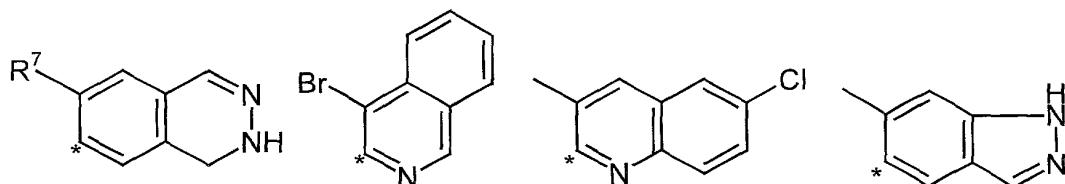


in which

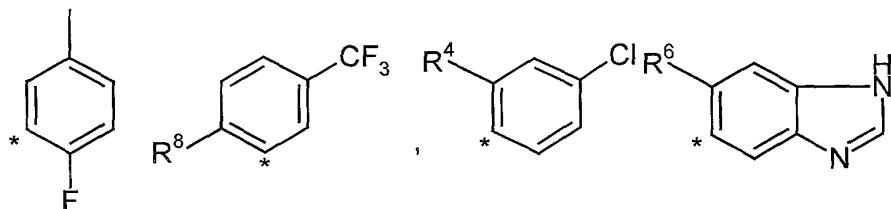
R^1 has the meaning of group



in which R^5 is chloro, bromo or the group $-\text{OCH}_3$,



in which R⁷ is -CH₃ or chloro,

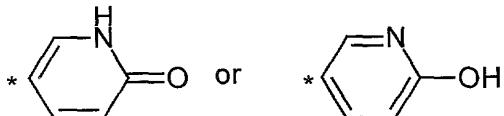


in which R⁸ is -CH₃, fluoro,
chloro or -CF₃

in which R⁴ is fluoro,
chloro, bromo, -CF₃,
-N=C, -CH₃, -OCF₃ or
-CH₂OH

in which R⁶ is
-CH₃ or chloro

R² has the meaning of pyridyl or the group



and

R³ has the meaning of hydrogen or fluoro, as well as their isomers and salts.

17. (Amended) Pharmaceutical compositions according to claim[s] 1[-16] which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, and as compound II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, with the provisio that compound I is not identically to compound II.

18. (Amended) Pharmaceutical compositions according to claim[s] 1[-17] which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium

hydrogen succinate and as compound II sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate.

19. (Amended) Pharmaceutical compositions according to claim[s] 1[-17] which comprise as compound I mAB 4301-42-35 and as compound II sTie2, and/ or scFv-tTF conjugate.

20. (Amended) Pharmaceutical compositions according to claim[s] 1[-17] which comprise as compound I scFv-tTF conjugate and as compound II sTie2 and/ or mAB 4301-42-35.

21. (Amended) Pharmaceutical compositions according to claim[s] 1[-17] which comprise as compound I L19 scFv-tTF conjugate and as compound II sTie2.

22. (Amended) Use of pharmaceutical compositions according to claim[s] 1[-21], for the production of a medicament for the treatment of tumors, cancers, psoriasis, arthritis, such as rheumatoide arthritis, hemangioma, angiofibroma, eye diseases, such as diabetic retinopathy, neovascular glaucoma, kidney diseases, such as glomerulonephritis, diabetic nephropathie, maligneous nephrosclerosis, thrombic microangiopathic syndrome, transplantation rejections and glomerulopathy, fibrotic diseases, such as cirrhotic liver, mesangial cell proliferative diseases, arteriosclerosis, damage of nerve tissues, suppression of the ascites formation in patients and suppression of VEGF oedemas.